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*Published in:*  
Investigative ophthalmology & visual science

*DOI:*  
[10.1167/iovs.15-18016](https://doi.org/10.1167/iovs.15-18016)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2015

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Wostyn, P., De Groot, V., Van Dam, D., Audenaert, K., Killer, H. E., & De Deyn, P. P. (2015). Glaucoma and the Role of Cerebrospinal Fluid Dynamics. *Investigative ophthalmology & visual science*, 56(11), 6630-6631. <https://doi.org/10.1167/iovs.15-18016>

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## Glaucoma and the Role of Cerebrospinal Fluid Dynamics

We read with great interest the article by Zhang et al.<sup>1</sup> entitled "Axonal Transport in the Rat Optic Nerve Following Short-Term Reduction in Cerebrospinal Fluid Pressure or Elevation in Intraocular Pressure," published recently in *Investigative Ophthalmology & Visual Science*. We appreciate the authors for their study and their efforts to explore potential mechanisms for glaucomatous damage related to low cerebrospinal fluid pressure (CSFP). However, we feel that an issue described in their article deserves further discussion.

In this study, the influence of short-term reduction in CSFP as compared with short-term elevation in IOP on axonal transport was investigated using experimental rat models.<sup>1</sup> The authors found that in both short-term lowering of CSFP and short-term rise in IOP, both the orthograde axoplasmic flow and the retrograde axonal transport in the retinal ganglion cell axons was impeded. However, the retinal layers, including the retinal ganglion cell layer, appeared grossly intact in the low-CSFP study group. According to the authors, one explanation could be that the experimental short-term reduction in CSFP only temporarily impeded the axoplasmic flow without leading to retinal ganglion cell loss. The authors further noted that the model of an acute reduction in CSFP is not a correct surrogate for a chronic reduction or intermittently low CSFP in patients. They emphasized that the results of their study could not be taken as proof that low CSFP is associated with the pathogenesis of glaucomatous optic neuropathy.

We believe there is still another possible explanation for the absence of retinal ganglion cell loss in the low-CSFP rat model that merits further discussion. Regardless of the fact that the effects of acute CSFP reduction on retinal ganglion cells may differ in important ways from those observed after longer-duration CSFP reduction or with repeated insults, there may be a substantial difference in CSF dynamics between the low-CSFP rat model in the current study and the low-CSFP situation in patients with glaucoma. A growing body of evidence indicates that CSFP is lower in patients with primary open-angle glaucoma (POAG) when compared with nonglaucomatous control subjects and, additionally, is lower in the normal-tension versus the high-tension form of POAG.<sup>2-4</sup> As noted by the authors, a reduction in CSFP may potentially reduce the turnover of the orbital CSF, which, theoretically, may cause an accumulation of waste material.<sup>1</sup> Our group recently proposed this hypothesis and speculated that the lower CSFP reported in normal-tension glaucoma (NTG) patients could be an indicator of CSF circulatory failure.<sup>5</sup> This CSF circulatory dysfunction could ultimately result in reduced clearance of toxic substances in the subarachnoid space surrounding the optic nerve and lead to glaucomatous damage.<sup>5</sup> In patients with NTG, the low CSFP may indeed result from decreased CSF production, thereby reducing CSF turnover. It should be stressed, however, that a decreased CSFP can be the consequence of decreased CSF production or reduced resistance to CSF outflow. Indeed, the CSFP is built up by the equilibrium between the production and outflow of CSF.<sup>5</sup> With regard to the low-CSFP situation in patients with glaucoma, it is important to note that a recent study found that CSFP decreases significantly and steadily after age 50.<sup>6</sup> This parallels the

rise in prevalence of glaucoma with increasing age.<sup>6</sup> There is no reported evidence that CSF outflow resistance decreases with age, rather most studies report CSF outflow resistance increases<sup>6,7</sup>; however, there is evidence that the CSF production decreases with age.<sup>6,8</sup> Therefore, the lower CSFP reported in NTG patients could be an indicator of decreased CSF production and turnover.<sup>5</sup>

The low-CSFP rat model in the current study, however, lowers CSFP by reducing the CSF outflow resistance. Indeed, for the rats of the low-CSFP study group, CSF was aspirated every 15 minutes over a study period of 6 hours.<sup>1</sup> Such continuous aspiration of CSF reduces the CSF outflow resistance and may improve CSF turnover. Theoretically, this could provide a protective effect against glaucomatous damage due to enhanced removal of potentially neurotoxic waste products that accumulate in the optic nerve. Therefore, a possible explanation for the absence of retinal ganglion cell loss in the low-CSFP rat model could be altered CSF dynamics related to CSF drainage, thereby reducing the CSF outflow resistance and improving the CSF flow. Obviously, additional research is needed to substantiate this interpretation.

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Citation: *Invest Ophthalmol Vis Sci*. 2015;56:6630–6631.  
doi:10.1167/iovs.15-18016